to acetylhymenograndin (**3b**).

Experimental Section

Isolation of 2 and 3b. Aerial parts of *Hymenoxys insignis* (Gray ex Wats) Cockll. were collected on August 2, 1975, on a mountainside above Cerro Potosi, north of Galeana, Nueva Leon, Mexico (Bierner No. 51358, on deposit in the herbarium in the University of Tennessee), dried, ground, and extracted with acetone in a Soxhlet apparatus. To avoid possible rearrangement of labile sesquiterpene lactones, we spotted the crude extract, 11.3 g, on several preparative TLC plates coated with silica gel (60 GF: 254–366, EM reagent, 2 mm thickness) and developed by using the solvent system MeOH–$CHCl_3$ (1:49). Examination under UV light showed five bands, none of which contained hymenovin. Fraction I contained waxy material which included sitosterol. Fraction II (1.65 g) on further purification with the same solvent system yielded a fraction (0.27 g) whose IR spectrum exhibited a γ-lactone band. Preparative TLC of this material (EtOAc–hexane) gave two bands which upon extraction yielded 31 mg of hymenosignin (R_f 0.3) and 46 mg of acetylhymenograndin (R_f 0.2). Fraction III contained no lactones and is still being investigated. TLC examination of fractions IV and V indicated the presence of a complex mixture of flavonoids.

Hymenosignin (**2**) was recrystallized from benzene–hexane: mp 111–113 °C; $[\alpha]_D$ +10.8° (*c* 0.014 75, $CHCl_3$); IR ($CHCl_3$) 1765, 1720, 1175, 1090, 1020 cm^{-1}. The molecular ion was extremely weak but could be detected by chemical ionization mass spectrometry and was measured by the peak-matching procedure.

Anal. Calcd for $C_{20}H_{30}O_5$: mol wt 350.2093. Found: mol wt (mass spectrometry) 350.2093.

Significant peaks in the low-resolution mass spectrum appeared at *m/e* 248 ($M^+ - C_5H_{10}O_2$), 233 ($M^+ - C_5H_{10}O_2 - CH_3$), 205, 203, 175, 148 (base peak), 135, 122, 118, 85 (C_5H_9O).

Acetylhymenograndin (**3b**) was a colorless gum which had the following: IR ($CHCl_3$) 1752, 1740 (br), 1260, 1230 cm^{-1}; UV (MeOH) λ_{max} 212 nm (ε 7850); $[\alpha]_D$ +60° (*c* 0.0160, $CHCl_3$); CD (MeOH) $[\theta]_{249}$ −5250, $[\theta]_{212}$ +33 500 (last reading).

Anal. Calcd for $C_{21}H_{28}O_8$: mol wt 408.1789. Found: mol wt (mass spectrometry) 408.1789.

Other significant peaks in the high-resolution mass spectrum appeared at *m/e* (relative intensity) 348 ($C_{19}H_{24}O_6$, 7.3), 306 ($C_{17}H_{22}O_5$, 36.4), 264 ($C_{15}H_{20}O_4$, 24.5), 246 ($C_{15}H_{18}O_3$, 71.6).

Acetylation of hymenograndin (**3a**) in the manner described earlier[13] gave a substance identical in all respects (TLC, IR, NMR at 270 MHz) with **3b**. To 200 mg of this material in 5 mL of MeOH was added with stirring and cooling in an ice bath 20 mg of $NaBH_4$ over a period of 30 min. After an additional 24 h at room temperature the precipitated product, 180 mg, was filtered and recrystallized from EtOAc. The product was identical in all respects (melting point, TLC, NMR at 270 MHz) with authentic hymenolane (**6**).

Autumnolide (**5**) was available from earlier work;[19a] CD (MeOH) $[\theta]_{249}$ −5250, $[\theta]$ 33 500 (last reading).

X-ray Analysis of 3a. Single crystals of hymenograndin were prepared by slow crystallization from MeOH. They belonged to space group $P2_12_12_1$, with a = 9.623 (3) Å, b = 11.135 (2) Å, c = 18.343 (4) Å, and d_{calcd} = 1.238 g cm^{-3} for Z = 4 ($C_{19}H_{26}O_7$, mol wt 366.41). The intensity data were collected on a Hilger–Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). A crystal measuring approximately 0.15 × 0.20 × 0.6 mm was used for data collection; the data were not corrected for absorption (μ = 7.9 cm^{-1}). A total of 1540 reflections were measured for $\theta < 57°$ of which 1452 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[24] and was refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the heavier atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were used in the structure-factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.034 and R_w = 0.042 for the 1452 observed reflections. The final difference map had no peaks greater than ±0.2 $Å^{-3}$.

X-ray Analysis of 2. Single crystals of **2** were prepared by slow crystallization from benzene–hexane. They belonged to space group $P2_12_12_1$, with a = 10.248 (3) Å, b = 10.699 (5) Å, c = 18.220 (5) Å, and d_{calcd} = 1.165 g cm^{-3} for Z = 4 ($C_{20}H_{30}O_5$, mol wt 350.46). The procedure used was the same as described in the previous paragraph: crystal of approximately 0.25 × 0.5 × 0.6 mm, no absorption correction (μ = 6.8 cm^{-1}), 1562 reflections of which 1383 were considered observed. The final discrepancy indices were R = 0.069 and R_w = 0.086 for the 1383 observed reflections. The final difference map had no peaks greater than ±0.3 $Å^{-3}$.

Acknowledgment. We wish to thank Dr. H. L. Kim for a sample of hymenolane.

Registry No. **2**, 72264-71-2; **3a**, 51292-55-8; **3b**, 72264-72-3; **5**, 20505-32-2; **6**, 62121-29-3.

Supplementary Material Available: Final atomic parameters (Table V), anisotropic thermal parameters (Table VI), bond lengths (Table VII), bond angles (Table VIII), and selected torsion angles (Table IX) for **2** and Tables X–XIV listing the same parameters, respectively, for **3a** (10 pages). Ordering information is given on any current masthead page.

(24) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1977**, *27*, 368.

Thiophene Systems. 3. Synthesis of Thieno[3,4-*b*][1,5]benzoxazepin-10-one and Thieno[3,4-*b*][1,5]benzothiazepin-10-one[1,2]

Jeffery B. Press,* Nancy H. Eudy, and Sidney R. Safir

Cardiovascular-CNS Disease Research Section, American Cyanamid Company, Medical Research Division, Lederle Laboratories, Pearl River, New York 10965

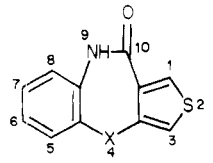
Received October 3, 1979

In an intensive investigation of novel tricyclic systems, several synthetic routes were attempted to prepare the title compounds. Condensation of either *o*-aminophenol (**5**) or *o*-aminobenzenethiol (**6**) with keto ester **4** gave **7** or **8**, respectively, the products of undesired reaction orientation. In an alternative approach, acid chloride **13** condensed with **5** to give amide **14** which gave title lactam **1** by the action of polyphosphoric acid. Other attempted methods for closing **14** to **1** were less efficient. Reaction of **13** with **6** gave bis-acyl derivative **17** or benzothiazole **18**, depending on reaction conditions. Reaction of disulfide **19** with **13** gave bis-amide **20** which was cleaved to mercaptan **21** with sodium borohydride. Title lactam **2** as well as **18** formed when **21** was treated with polyphosphoric acid. Both **1** and **2** were selectively chlorinated at the 3-position to give **23** and **24**, respectively.

As part of a continuing effort to develop novel tricyclic systems, the syntheses of thieno[3,4-*b*][1,5]benzoxazepin-10-one (**1**) and thieno[3,4-*b*][1,5]benzothiazepin-10-one (**2**) and their derivatives were subjects of intensive investiga-

0022-3263/80/1945-0497$01.00/0

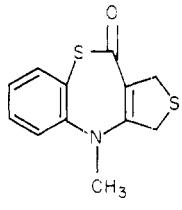
tion in these laboratories. Such thiophene systems,



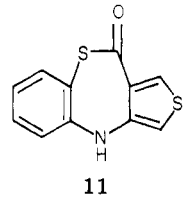
1, X = O
2, X = S
3, X = NH

without substitution in the 1- and 3-positions, appear, a priori, difficult to prepare by conventional chemistry inasmuch as reactions usually occur α to the sulfur atom of thiophene. In a previous report,[3] synthesis of the similar thieno[3,4-*b*][1,5]benzodiazepin-10-one (**3**) was described wherein *o*-phenylenediamine condensed with methyl tetrahydro-4-oxothiophene-3-carboxylate[4] (**4**) to give the desired ring system which was easily oxidized to **3**.

It was first hoped that **1** or **2** might be prepared by direct condensation of **4** with either *o*-aminophenol (**5**) or *o*-aminobenzenethiol (**6**), respectively, in a manner analogous to the synthesis of **3**. Acid-catalyzed condensation of **4** with **5** resulted in formation of enamine **7**, a product of undesired orientation, as the sole isolable product in good yield. In the case of **4** condensing with **6**, reaction again occurred with undesired orientation, leading to the formation of the ring-closed enamino thiolactone **8** in modest yield. Unequivocal assignment of structure **8** was rendered difficult by the unexpectedly low carbonyl absorption at 1595 cm^{-1} in the IR spectrum and the unremarkable ^1H NMR spectrum. Chemical transformation of **8** with sodium hydride/methyl iodide gave thiolactone **9**. The structure of **9** was supported by a three-proton singlet in the ^1H NMR spectrum typical of quaternary *C*-methyl substitution as well as an IR absorption at 1740 cm^{-1} consistent with the thiolactone moiety. Thiolactone **9** was different in all respects from isomer **10** prepared by direct condensation of **4** with *o*-(methylamino)benzenethiol; **10** also displayed an unusually low carbonyl absorption in the IR spectrum at 1600 cm^{-1}. Thiolactone **8** was oxidized with difficulty by the action of sulfuryl chloride to the thiophene derivative **11** which exhibited the expected spectral properties.



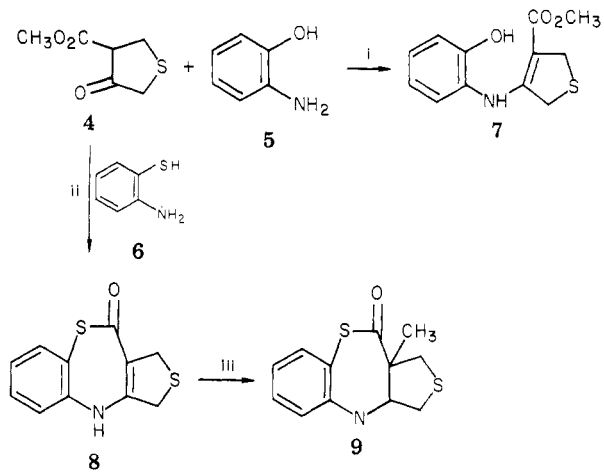
10



11

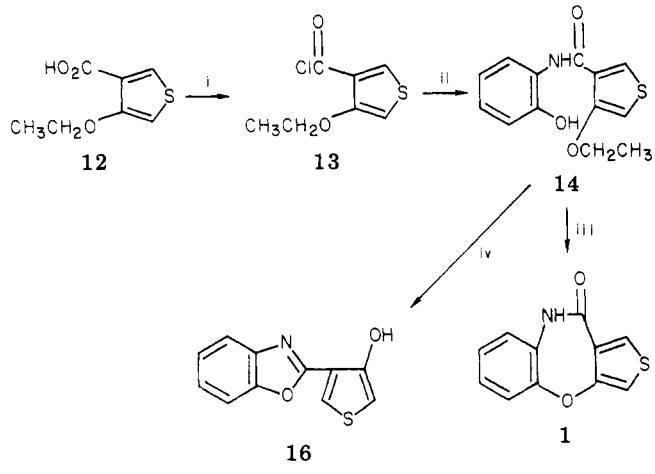
In order to prepare targets **1** and **2**, it was obviously necessary to use another approach wherein the lactam linkage could be formed in preference to the enamine linkage already noted. For the preparation of **1**, ethoxy acid[1] **12** was converted to acid chloride **13** with thionyl chloride, and **13** was subsequently condensed with **5** in methylene chloride with triethylamine to yield amide **14**. Amide **14** possesses an enol ether-like moiety which has been shown to be acid labile in similar molecules.[1] As a

Scheme I[a]



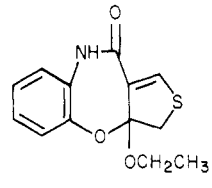
[a] i, $PhCH_3$/*p*-TSA/Δ; ii, $PhCH_3$/AcOH/Δ; iii, NaH/CH_3I/DMF.

Scheme II[a]



[a] i, $SOCl_2$; ii, **5**/Et_3N; iii, PPA/Δ; iv, pyr·HCl/Δ.

direct consequence of this lability, treatment of **14** with polyphosphoric acid at 120 °C was effective in causing ring closure to **1** presumably through the intermediacy of ketal **15**. Other acidic agents studied to effect ring closure of



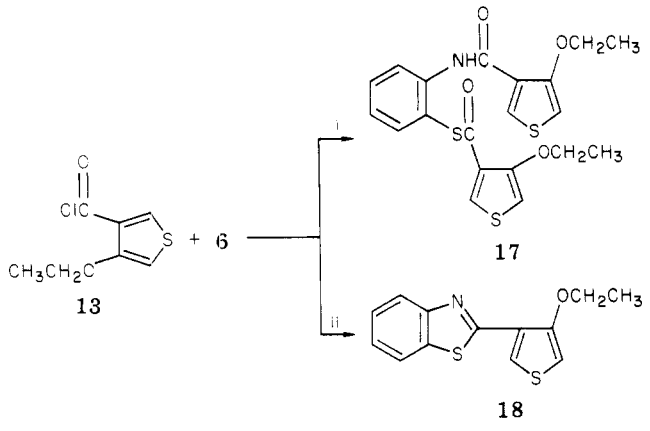
15

14 were less satisfactory. Sulfuric acid caused formation of **1** in poor (≤2%) yield. When **14** was treated with molten pyridine hydrochloride,[5] exclusive formation of **16** was observed as a result of nucleophilic condensation of the phenolic hydroxyl upon the amide carbonyl, subsequent dehydration, and cleavage of the ether linkage by the reagent.

With the straightforward preparation of **1** as outlined above, attention was turned to the synthesis of **2**. Unfortunately, condensation of acid chloride **13** with *o*-aminobenzenethiol (**6**) proved to be extremely capricious.

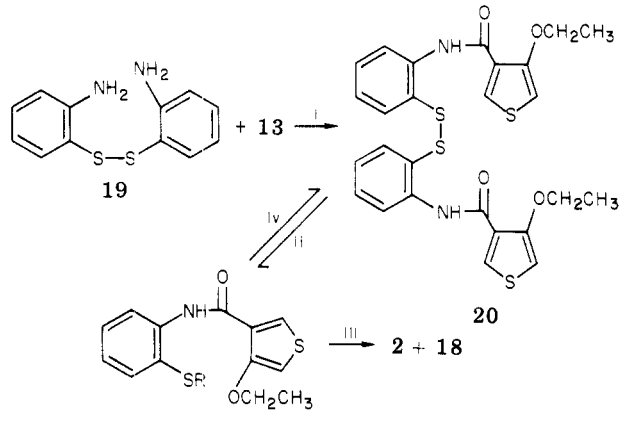
(1) For the previous paper in this series see: Press, J. B.; Hofmann, C. M.; Safir, S. R. *J. Org. Chem.* **1979**, *44*, 3292.
(2) These intermediates are the subjects of U.S. Patent 4 144 235.
(3) Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. *J. Med. Chem.* **1979**, *22*, 725.
(4) (a) Woodward, R. B.; Eastman, R. N. *J. Am. Chem. Soc.* **1946**, *68*, 2232. (b) Hromatka, O.; Binder, D.; Eichinger, K. *Monatsh. Chem.* **1973**, *104*, 1520.
(5) (a) Similar closures to form diphenyl ethers have been reported. For example: Flad, G.; Demerseman, P.; Roger, R. *Bull. Soc. Chim. Fr.* **1976**, 1823. (b) Henrio, G.; Morel, J.; Pastour, P. *Tetrahedron* **1977**, *33*, 191.

Scheme III[a]



[a] i, Et_3N/CH_2Cl_2; ii, Et_3N/PhH.

Scheme IV[a]

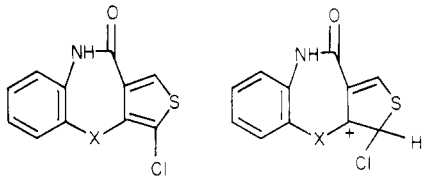


[a] i, Et_3N/CH_2Cl_2; ii, $NaBH_4$/EtOH or Na_2S/H_2O/MeOH; iii, PPA/Δ; iv, air.

Reaction of 6 and 13 in methylene chloride with triethylamine caused formation of bis-acyl adduct 17 in high yield. The same reaction performed in benzene as solvent caused formation of benzothiazole 18. Attempts to alter the outcome of reaction by varying the ratio of 6:13 failed. Apparently, the highly reactive mercaptan moiety of 6 adversely affected the desired course of reaction, and suitable methods of protection of the mercaptan were required.

Toward this end, 13 was condensed with disulfide 19 to give bis amido disulfide 20 in excellent yield. Disulfide 20 was reduced to mercaptan 21 with aqueous sodium sulfide or preferably a large excess of sodium borohydride. Methylation of the mercaptide of 21 gave 22 which was identical with material prepared by direct condensation of 13 and 2-methylthioaniline. Mercaptan 21 was moderately stable and could be stored; however, upon exposure to air, 21 reverted to 20. This reversion was prevented by preparing 21 in situ and using it immediately in subsequent reactions. Closure of 21 proceeded in polyphosphoric acid at 120 °C to give the desired thiazepinone 2 and the previously isolated benzothiazole 18 in approximately equal amounts. Compounds 2 and 18 were easily separable by silica gel chromatography.

Both desired lactams 1 and 2 reacted smoothly with sulfuryl chloride to give chloro derivatives 23 and 24 exclusively. This high selectivity of halogenation arises presumably from the heteroatom stabilization of the incipient carbonium ion 25 and has been noted previously in similar thiophene systems.[1]



23, X = O
24, X = S

25

The synthetic schemes outlined herein allow preparation of lactams 1 and 2 as well as their chloro derivatives 23 and 24 in useful quantities. Conversion of these tricyclic intermediates to biologically active, novel CNS agents with potential neuroleptic and/or antidepressant activity will be the subject of a future report from these laboratories.[6]

Experimental Section

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All reported compounds are homogeneous by thin-layer chromatography analysis [Whatman K5F (5 × 10 cm) silica gel analytical plates]. ^1H NMR measurements were obtained on a Varian Associates HA-100A spectrometer and chemical shift values are reported in δ ($CDCl_3$ or Me_2SO_4-d_6) downfield from tetramethylsilane as the internal standard. Mass spectral measurements were made on an AEI MS-9 mass spectrometer. UV determinations were made in ethanol solvent with a Cary Model 14 recording spectrophotometer.

Methyl 2,5-Dihydro-4-(*o*-hydroxyanilino)thiophene-3-carboxylate (7). Methyl tetrahydro-4-oxothiophene-3-carboxylate[4] (21.8 g, 0.2 mol), *o*-aminophenol (32 g, 0.2 mol), and *p*-toluenesulfonic acid (0.5 g) were dissolved in toluene (200 mL), and the solution was refluxed using a Dean–Stark water separator for 4 h. The mixture was concentrated to half-volume and cooled to 0 °C, and the resultant yellow crystals were collected (32.9 g, 66%). Recrystallization from ethanol gave the analytical sample: mp 149.5–150.5 °C; UV 208, 230, 315 nm; ^1H NMR 9.14 (br s, 1 H, NH), 7.0 (m, 4 H, aromatic H), 6.33 (br s, 1 H, OH), 3.80 (m, 7 H, CH_3, CH_2S); mass spectrum *m/e* 251 (M^+).

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.30; H, 5.21; N, 5.57; S, 12.70. Found: C, 57.55; H, 5.33; N, 5.71; S, 12.59.

1,4-Dihydro-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepin-10-one (8). Methyl tetrahydro-4-oxothiophene-3-carboxylate[4] (160 g, 1.0 mol) and *o*-aminothiophenol (125 g, 1.0 mol) were refluxed in toluene (1 L) containing acetic acid (3 mL) and water (3 mL) for 6 h. Concentration to half-volume and cooling to 5 °C gave yellow crystals (43.85 g, 19%) which were recrystallized from ethanol to give the analytical sample: mp 248–251 °C; ^1H NMR 10.2 (br s, 1 H, NH), 7.50 (m, 4 H, aromatic H), 4.00 (s, 2 H), 3.65 (s, 2 H, both CH_2S); mass spectrum *m/e* 235 (M^+).

Anal. Calcd for $C_{11}H_9NOS_2$: C, 56.10; H, 3.85; N, 5.95; S, 27.20. Found: C, 56.22; H, 4.00; N, 5.94; S, 27.18.

1,10a-Dihydro-10a-methyl-3*H*,10*H*-thieno[3,4-*c*][1,5]-benzothiazepin-10-one (9). A mixture of 8 (7.00 g, 0.030 mol) and sodium hydride (1.39 g, 57% suspension, 0.033 mol) was stirred in dimethylformamide (250 mL) for 15 min. Methyl iodide (4.98 g, 0.035 mol) was added and the mixture was stirred for 2 h. The reaction mixture was diluted with water (500 mL) and extracted with methylene chloride (3×), and the combined organic layers were concentrated. The residue was eluted through a silica gel column (300 g) with 20% ethyl acetate–hexane to give the product as a yellow oil (7.7 g). Crystallization from cyclohexane (75 mL) gave the pure product, 5.16 g (70%), as bright yellow crystals: mp 84–85 °C; UV 218, 255, 290 nm; ^1H NMR 7.6 (m, 4 H, aromatic H), 3.50 (dq, 4 H, CH_2S), 1.77 (s, 3 H, CH_3); mass spectrum *m/e* 249 (M^+).

Anal. Calcd for $C_{12}H_{11}NOS_2$: C, 57.80; H, 4.45; N, 5.62; S, 25.72. Found: C, 58.20; H, 4.83; N, 5.53; S, 25.72.

1,4-Dihydro-4-methyl-3*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepin-10-one (10). Methyl tetrahydro-4-oxothiophene-3-

(6) Press, J. B.; Eudy, N. H.; Hofmann, C. M.; Safir, S. R., manuscript in preparation.

carboxylate (16.0 g, 0.10 mol), *N*-methyl-*o*-aminothiophenol (13.9 g, 0.10 mol), acetic acid (0.5 mL), and water (0.5 mL) were refluxed in toluene (100 mL) for 6 h. Cooling overnight at 0 °C provided an orange-yellow solid (5.00 g, 20%) which was recrystallized from ethanol to give the analytical sample: mp 240–241 °C; UV 215, 240, 373 nm; ^{1}H NMR 7.50 (m, 4 H, aromatic H), 4.45 (s, 2 H, CH_2), 3.91 (s, 3 H, CH_3), 3.46 (s, 2 H, CH_2S); mass spectrum *m/e* 249 (M^+).

Anal. Calcd for $C_{12}H_{11}NOS_2$: C, 57.80; H, 4.45; N, 5.62; S, 25.72. Found: C, 57.79; H, 4.72; N, 5.47; S, 25.54.

4*H*,10*H*-Thieno[3,4-*c*][1,5]benzothiazepin-10-one (11). A suspension of **8** (4.70 g, 0.02 mol) in 1,2-dichloroethane (200 mL) was treated with sulfuryl chloride (2.83 g, 0.021 mol) dropwise at 0 °C. The mixture was refluxed 4 h and stirred overnight at room temperature. The mixture was filtered through magnesium silicate with chloroform eluant to give a yellow solid product after concentration (1.44 g, 31%). The analytical sample was prepared by recrystallization from methylcyclohexane: mp 138.5–139 °C; UV 215, 315 nm; ^{1}H NMR 10.63 (br s, 1 H, NH), 7.62 (d, 1 H, thiophene H), 7.50 (m, 4 H, aromatic H), 6.45 (d, 1 H, thiophene H); mass spectrum *m/e* 233 (M^+).

Anal. Calcd for $C_{11}H_7NOS_2$: C, 56.63; H, 3.02; N, 6.00; S, 27.49. Found: C, 56.48; H, 2.98; N, 5.98; S, 27.29.

3-Ethoxy-3-thiophenecarbonyl Chloride (13). 4-Ethoxythiophene-3-carboxylic acid[1] (10.3 g, 0.060 mol) was treated with thionyl chloride (12 mL) dropwise over 0.5 h. The reaction was warmed to 100 °C for 2 h, excess reagent was removed with a water aspirator, and the residue was vacuum distilled to give the product as pale yellow crystals: bp 125–127 °C (0.35 mmHg); 9.30 g (82%). The product was unstable for storage and the yield was variable in the 50–90% range: IR 1785 cm^{-1}; ^{1}H NMR 8.40 (d, 1 H), 6.40 (d, 1 H, both thiophene H), 4.15 (q, 2 H, CH_2), 1.48 (t, 3 H, CH_3).

4-Ethoxy-2′-hydroxythiophene-3-carboxanilide (14). A solution of **13** (9.00 g, 0.0472 mol) in methylene chloride (100 mL) was added dropwise to a suspension of *o*-aminophenol (5.15 g, 0.0472 mol) in methylene chloride (100 mL) containing triethylamine (4.8 g, 0.0472 mol), and the mixture was stirred overnight. The precipitate was collected by filtration, triturated with water for 3 h, and dried to give the product as a tan solid, 8.70 g (70%). Recrystallization from methylene chloride/petroleum ether gave the analytical material as white crystals: mp 230–231 °C; UV 205, 245, 270, 278, 300 nm; ^{1}H NMR 10.1 (br s, 1 H, OH), 9.9 (s, 1 H, NH), 8.35 (d, 1 H, *o*-aromatic H), 8.12 (d, 1 H, thiophene H), 6.85 (m, 4 H, thiophene and aromatic H), 4.20 (q, 2 H, CH_2), 1.5 (t, 3 H, CH_3); mass spectrum *m/e* 263 (M^+).

Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 58.87; H, 5.08; N, 5.19; S, 12.27.

Thieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one (1). A mixture of **14** (6.59 g, 0.025 mol) and polyphosphoric acid (125 g) was ground intimately and warmed to 120 °C for 1.5 h, cooled to room temperature, diluted with water (300 mL), and cooled to 5 °C. The precipitate (5.04 g) was sublimed to give the pure white product: 3.45 g (64%); mp 239.5–241 °C; UV 215, 255 nm; ^{1}H NMR 10.2 (br s, 1 H, NH), 8.10 (d, 1 H, thiophene H), 7.15 (m, 5 H, thiophene, aromatic H); mass spectrum *m/e* 217 (M^+).

Anal. Calcd for $C_{11}H_7NO_2S$: C, 60.81; H, 3.25; N, 6.45; S, 14.76. Found: C, 60.61; H, 3.33; N, 6.33; S, 14.67.

4-(2-Benzoxazolyl)thiophen-3-ol (16). Pyridine hydrochloride (8.4 g, 0.076 mol) and **14** (2.0 g, 0.0076 mol) were ground together and heated to 200 °C for 1.5 h. (There was complete disappearance of **14** as evidenced by TLC analysis.) The reaction mixture was cooled and diluted with ice water (50 mL), and the crude product was collected by filtration (1.05 g). Extraction of the solid with methylene chloride in a Soxhlet extractor, filtration of the extract through magnesium silicate, and recrystallization of the eluate from methylene chloride/hexanes gave the analytical product as white crystals: mp 104–105 °C; ^{1}H NMR 9.75 (br s, 1 H, OH), 7.93 (d, 1 H, thiophene H), 7.72 (m, 1 H), 7.57 (m, 1 H), 7.39 (m, 2 H, all aromatic H), 6.48 (d, 1 H, thiophene H); mass spectrum *m/e* calcd for $C_{11}H_7NSO_2$, 217.0198; *m/e* found, 217.0190.

***S*-[*o*-(4-Ethoxythiophene-3-carboxamido)phenyl] 4-Ethoxythiophene-3-carbothioate (17).** *o*-Aminothiophenol (5.46 g, 0.0436 mol) in methylene chloride (100 mL) was treated dropwise with a solution of **13** (8.30 g, 0.0436 mol) and triethylamine (6.0 mL, 0.0436 mol), and the mixture was stirred overnight. A precipitate was removed by filtration and the filtrate was concentrated and eluted through a silica gel column (800 g) with 20% acetone–hexanes to give a yellow foam, 4.5 g (48% on the basis of acid chloride). The analytical sample was obtained by recrystallization from ethanol: mp 136–138 °C; ^{1}H NMR 9.72 (br s, 1 H, NH), 8.48 (m, 1 H, aromatic H), 8.32 (d, 1 H), 8.20 (d, 1 H, both thiophene H), 7.48, 7.19 (m, 3 H, aromatic H), 6.78 (t, 2 H, thiophene H), 4.05 (q, 4 H, CH_2), 1.36 (t, 3 H, CH_3), 1.16 (t, 3 H, CH_3); mass spectrum *m/e* 433 (M^+).

Anal. Calcd for $C_{20}H_{19}NO_4S_3$: C, 55.41; H, 4.42; N, 3.23; S, 22.19. Found: C, 55.23; H, 4.27; N, 3.50; S, 22.30.

2,2′-Dithiobis(4-ethoxythiophene-3-carboxanilide) (20). 2,2′-Dithiobis(aniline) (7.44 g, 0.03 mol) and triethylamine (6.1 g, 0.06 mol) in methylene chloride (100 mL) were treated dropwise with a solution of **13** (11.45 g, 0.06 mol) as above. The reaction mixture was concentrated and treated with ethyl acetate (50 mL), and the precipitate was collected. The solid was triturated with water (50 mL) and dried to give the crude yellow product (14.28 g, 86%) which was recrystallized from methylene chloride–petroleum ether to give the analytical material: mp 139–141 °C; ^{1}H NMR 10.0 (br s, 2 H, NH), 8.45 (d, 2 H, aromatic H), 8.08 (d, 2 H, thiophene H), 7.10 (m, 6 H, aromatic H), 6.30 (d, 2 H, thiophene H), 4.15 (q, 4 H, CH_2), 1.45 (t, 6 H, CH_3); mass spectrum *m/e* 556 (M^+).

Anal. Calcd for $C_{26}H_{24}N_2O_4S_4$: C, 56.09; H, 4.35; N, 5.03; S, 23.04. Found: C, 56.01; H, 4.29; N, 4.94; S, 22.89.

4-Ethoxy-2′-mercaptothiophene-3-carboxanilide (21). Disulfide **20** (8.00 g, 0.0144 mol) in ethanol (400 mL) was treated with sodium borohydride (1.50 g, excess), and the mixture was refluxed overnight. The mixture was concentrated and diluted with aqueous acetic acid and methylene chloride, and the organic layer was separated, washed with water and aqueous sodium bicarbonate, and dried over sodium sulfate. The organic layer was then concentrated to give the product as a yellow oil which solidified upon standing (8.00 g, 100%). The analytical sample was prepared from methylene chloride/petroleum ether as yellow needles, mp 73.5–74.5 °C. In general, the mercaptan was not isolated but rather the reaction mixture was concentrated to dryness and immediately treated in the next step: ^{1}H NMR 9.70 (br s, 1 H, NH), 8.35 (d, 1 H, aromatic H), 8.18 (d, 1 H, thiophene H), 7.30 (m, 3 H, aromatic H), 6.35 (d, 1 H, thiophene H), 4.22 (q, 2 H, CH_2), 3.19 (s, 1 H, SH), 1.54 (t, 3 H, CH_3); mass spectrum *m/e* 279 (M^+).

Anal. Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01; S, 22.95. Found: C, 55.74; H, 4.68; N, 5.13; S, 22.97.

4-Ethoxy-2′-(methylthio)thiophene-3-carboxanilide (22). 2-(Methylthio)aniline (4.17 g, 0.03 mol) was treated as above with **13** (5.70 g, 0.03 mol) in methylene chloride and worked up as before to provide the product as a yellow solid, 4.40 g (50%). The analytical sample was obtained from hexanes: mp 83–84.5 °C; ^{1}H NMR 9.98 (br s, 1 H, NH), 8.45 (m, 1 H, aromatic H), 8.18 (d, 1 H, thiophene H), 7.28 (m, 3 H, aromatic H), 6.35 (d, 1 H, thiophene H), 4.24 (q, 2 H, CH_2), 2.38 (s, 3 H, SCH_3), 1.56 (t, 3 H, CH_3); mass spectrum *m/e* 293 (M^+).

Anal. Calcd for $C_{14}H_{15}NO_2S_2$: C, 57.31; H, 5.15; N, 4.77; S, 21.86. Found: C, 57.35; H, 4.98; N, 4.87; S, 21.78.

If disulfide **20** (0.56 g, 0.001 mol) was suspended in methanol (50 mL) and treated with aqueous sodium sulfide (1 g, excess) for 2 h in a manner reported by Buraway[7] and subsequently treated with sodium methoxide (0.11 g, 0.002 mol) and methyl iodide (0.19 mL, 0.003 mol) overnight, routine workup gave **22** identical with the product previously prepared (0.48 g, 87%).

Thieno[3,4-*b*][1,5]benzothiazepin-10(9*H*)-one (2) and 2-(4-Ethoxy-3-thienyl)benzothiazole (18). Mercaptan **21** (8.00 g, 0.0287 mol) was treated with polyphosphoric acid (100 g) at 120 °C for 2 h. After the mixture was cooled and diluted with ice water (400 mL), the precipitate (4.70 g) was collected and purified on a silica gel column (300 g) using 15% ethyl acetate–hexanes as the eluant. Benzothiazole **18** eluted first (2.13 g, 30%) and was recrystallized from hexanes to give the analytical sample: mp 107–108.5 °C; UV 210, 250, 258, 315 nm; ^{1}H NMR 8.22 (d, 1 H, thiophene H), 7.98 (m, 2 H, aromatic H), 7.38 (m, 2 H, aromatic H), 6.35 (d, 1 H, thiophene H), 4.21 (q, 2 H, CH_2), 1.53

(7) Buraway, A.; Turner, C. *J. Chem. Soc.* **1950**, 469.

(t, CH_3); mass spectrum m/e 261 (M^+).

Anal. Calcd for $C_{13}H_{11}NOS_2$: C, 59.74; H, 4.24; N, 5.36; S, 24.54. Found: C, 59.65; H, 4.24; N, 5.24; S, 24.05.

Benzothiazepinone **2** eluted next (2.50 g, 37%) and was purified from methylene chloride/petroleum ether to give the analytical product: mp 218–219 °C; UV 230, 250, 310 nm; ^1H NMR 10.30 (br s, 1 H, NH), 8.16 (d, 1 H, thiophene H), 7.61 (d, 1 H, thiophene H), 7.2 (m, 4 H, aromatic H); mass spectrum m/e calcd for $C_{11}H_7NOS_2$, 232.9969; m/e found, 232.9963.

Anal. Calcd for $C_{11}H_7NOS_2$: C, 56.63; H, 3.02; N, 6.00; S, 27.49. Found: C, 55.97; H, 3.12; N, 5.79; S, 27.21.

3-Chlorothieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one (23). A suspension of **1** (2.2 g, 0.01 mol) in chloroform (100 mL) was treated with sulfuryl chloride (0.9 mL, 0.01 mol) dropwise, and the mixture was stirred overnight. The product was collected by filtration (1.62 g, 64%) and melted at 258–260 °C: UV 210, 260 nm; ^1H NMR 10.28 (br s, 1 H, NH), 8.07 (s, 1 H, thiophene H), 7.20 (m, 4 H, aromatic H); mass spectrum m/e 251 (M^+).

Anal. Calcd for $C_{11}H_6ClNO_2S$: C, 52.49; H, 2.40; N, 5.57; S, 12.74; Cl, 14.09. Found: C, 52.66; H, 2.72; N, 5.44; S, 12.62; Cl, 14.03.

3-Chlorothieno[3,4-*b*][1,5]benzothiazepin-10(9*H*)-one (24). A suspension of **2** (2.33 g, 0.01 mol) in methylene chloride (40 mL) was treated with sulfuryl chloride (0.95 mL, 0.012 mol), and the mixture was refluxed for 2 h. After the mixture cooled to 0 °C, the precipitate was collected by filtration (2.15 g, 85%) and recrystallized from methylene chloride to give the analytical sample as white crystals: mp 287–288 °C; UV 205, 255 nm; ^1H NMR 10.40 (br s, 1 H, NH), 8.06 (s, 1 H, thiophene H), 7.25 (m, 4 H, aromatic H); mass spectrum m/e 267 (M^+).

Anal. Calcd for $C_{11}H_6ClNOS_2$: C, 49.34; H, 2.26; N, 5.23; S, 23.95; Cl, 13.24. Found: C, 49.34; H, 2.37; N, 5.33; S, 23.91; Cl, 13.50.

Acknowledgment. We acknowledge W. Fulmor and staff for spectral analyses, G. Morton for helpful insights on ^1H NMR spectra, and L. Brancone and staff for microanalytical elemental analyses.

Registry No. **1**, 70438-03-8; **2**, 70438-23-2; **4**, 2689-68-1; **5**, 95-55-6; **6**, 137-07-5; **7**, 72205-85-7; **8**, 72205-86-8; **9**, 72205-87-9; **10**, 72205-88-0; **11**, 72205-89-1; **12**, 70438-00-5; **13**, 70438-01-6; **14**, 70438-02-7; **16**, 72205-90-4; **17**, 72205-91-5; **18**, 72205-92-6; **19**, 1141-88-4; **20**, 70438-21-0; **21**, 70438-22-1; **22**, 72205-93-7; **23**, 70438-17-4; **24**, 70438-40-3; *N*-methyl-*o*-aminothiophenol, 21749-63-3; 2-(methylthio)aniline, 2987-53-3.

Synthesis of C-Ring-Functionalized A-Ring-Aromatic Trichothecane Analogues

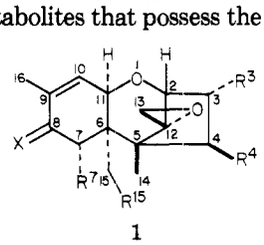
Wayne K. Anderson* and George E. Lee

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260

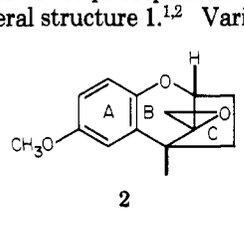
Received August 29, 1979

15,16-Dinor-4α-acetoxy-8-methoxy-6,8,10-trichothecatriene 12,13-epoxide (**11**) was prepared from 2α-(2-acetoxy-5-methoxyphenyl)-2β-methyl-3α-acetoxycyclopentanone (**8**) in three steps (bromination, DBN-induced cyclization, and spiroepoxidation). The cyclopentanone **8** was prepared from the hemiketal **6a** which was prepared from 2′-acetoxy-5′-methoxyacetophenone (**3f**) in a reaction sequence involving the boron trifluoride catalyzed aldol addition of 1,2-bis(trimethylsilyloxy)cyclobutene followed by a trifluoroacetic acid catalyzed pinacol rearrangement of the cyclobutanone intermediate.

The trichothecanes are a class of sesquiterpene fungal metabolites that possess the general structure **1**.[1,2] Various



1



2

members of this class have been demonstrated to possess a number of interesting biological properties, including significant antineoplastic activity.[1] We recently reported a synthesis of an A-ring aromatic trichothecane analogue, **2**,[3] and have subsequently shown that this compound possesses significant in vivo antileukemic activity (P388).[4]

We now wish to report a synthesis of A-ring aromatic trichothecane analogues that possess C-ring functionality analogous to the naturally occurring trichothecanes.

The strategy for the synthesis of C-ring functionalized compounds, like our previous approach, involves the assembly of the requisite A and C rings and subsequent cyclization of the B ring through the formation of the 1,2-ether bond. In the present approach, the A- and C-ring backbone was prepared using an aldol addition–pinacol rearrangement sequence.[5]

2′,5′-Dimethoxyacetophenone[6] (**3a**) was converted to the dimethyl ketal **3b** by treatment with 1 equiv of trimethyl orthoformate in refluxing absolute methanol containing a catalytic amount of *p*-toluenesulfonic acid monohydrate. A mixture of **3b** and 1,2-bis(trimethylsilyloxy)cyclobutene[7] in dichloromethane was treated with 2 equiv of boron trifluoride etherate at −78 °C, and the cyclopentadione **5a** was obtained in 39% yield along with 50–60% of the pi-

(1) (a) Bamburg, J. R. *Clin. Toxicol.* **1972**, *5*, 495. (b) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 64. (c) Rodricks, J. V.; Eppley, R. M. "Mycotoxins"; Purchase, I. F. H., Ed.; American Elsevier: New York, 1974; p 181. (d) Smalley, E. B.; Strong, F. M. *Ibid.*, 199. (e) Joffe, A. Z. *Ibid.*, 229. (f) Saito M.; Ohtsubo, K. *Ibid.*, 263. (g) Kupchan, S. M.; Jarvis, B. B.; Dailey, Jr., R. G.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, *98*, 7092.

(2) Baccharin has a β-epoxide in place of the 9,10-double bond.[1g]

(3) Anderson, W. K.; LaVoie, E. J.; Lee, G. E. *J. Org. Chem.* **1977**, *42*, 1045.

(4) Anderson, W. K.; Lee, G. E. *J. Med. Chem.*, in press.

(5) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961.

(6) (a) The Friedel–Crafts acylation of *p*-dimethoxybenzene in polyphosphoric acid–acetic acid gave **3a** in nearly twice the literature yield, **6b** when the reaction was conducted at 60–75 °C instead of 85 °C. (b) Horton, J. W.; Spence, J. J. *J. Am. Chem. Soc.* **1955**, *77*, 2894.

(7) Bloomfield, J. J.; Nolke, J. M. *Org. React.* **1976**, *23*, 259.

0022-3263/80/1945-0501$01.00/0